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## SHORT REPORT

## Regulatory Policies

# Temporary derogation from European environmental legislation for clinical trials of genetically modified organisms for coronavirus disease 2019

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## ABSTRACT

Attempts to streamline environmental procedures for those products containing or consisting of genetically modified organisms (GMOs) among the European Union (EU) Member States are ongoing but still need to be further developed. These procedures can be complex, resource-intensive and time-consuming. Some candidate vaccines currently under development for COVID-19 include genetically modified viruses, which may be considered GMOs. Given the public health emergency caused by the COVID-19 outbreak, on July 15, 2020, the European Parliament approved a temporary derogation of the European environmental requirements to facilitate that those clinical trials with GMOs intended to treat or prevent COVID-19 can start as soon as possible in Europe. This measure has been very controversial, since it could entail risks to human health and the environment, and could be seen as unfair for other products targeting unmet medical needs. With the adoption of this measure, the bottlenecks and obstacles for the development of innovative GMO-based medicines in the EU that the environmental legislation entails have become even more evident.

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## Environmental legislation in the European Union

Biological therapies comprise a wide range of product types, including advanced therapies and vaccines. Gene therapy medicinal products (GTMPs) are cutting-edge therapies and promise to treat indications ranging from rare genetic diseases to cancers. GTMPs treat disease by replacing, inactivating or introducing a recombinant nucleic acid sequence into the body, typically using a viral vector or through other carrier molecules. On the other hand, vaccines are a heterogeneous class of biological medicinal products aimed at the treatment or prophylaxis of infectious diseases and include not only classic vaccines consisting of attenuated or inactivated micro-organisms but also antigens produced through recombinant DNA technology, chimeric micro-organisms and live recombinant viral vectored vaccines. When a biological entity is capable of replication or of transferring altered genetic material, as is the case with many GTMPs and some vaccines, it is also considered a genetically modified organism (GMO).

The clinical use of these therapies might pose a risk since these products may enter the environment by unintended dispersal or via excretion by the patient. This dissemination could potentially spread the GMO further, and it could undergo genetic or phenotypic changes, infect,

reproduce, remain latent, compete with existing species or transfer its genetic material to other species, impacting human health and the environment. As a result, medicinal products consisting of or containing a GMO are regulated by environmental and human drug legislation in the European Union (EU), and all potential risks must be evaluated by conducting an environmental risk assessment (ERA) during the product's development. To conduct a clinical trial with a product based on a GMO, the sponsor needs to obtain not only authorization from the ethics committees and competent national health authorities (NHAs) where the study is going to take place but also an additional authorization to "release" or administer the GMO-containing medicinal product in that trial. To obtain this authorization, an ERA must be assessed and endorsed by the government authorities of each Member State in charge of GMO evaluations and responsible for the environment in each country.

In recent years, especially with the increased development of advanced therapies, the lack of harmonization among the European countries and the burden these environmental procedures entail for the sponsor have become notably evident. Although there is a common European framework in place, the environmental EU directives have been implemented differently across European countries. This fact has resulted in a resource-intensive process, above all for multicenter studies, as sponsors of clinical trials need to submit multiple requests for environmental authorizations to multiple competent authorities in different Member States, each with different requirements and ERA procedures that vary greatly from one Member State to another. The

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result is the generation of delays in clinical development, an increase in logistical hurdles at country level and higher costs [1]. The European Commission recognized in 2018 the handicaps of these procedures in the EU and initiated several dialogues with the NHAs with the aim to unify the interpretation of the GMO framework. As a result, common position documents for genetically modified human cells and for products containing adeno-associated viruses were recently endorsed by most NHAs. Nevertheless, this approach is still not enough, and this procedure remains substantially burdensome.

### Temporary changes in environmental legislation due to the coronavirus disease 2019 pandemic

Coronavirus disease 2019 (COVID-19) has rapidly developed into a worldwide pandemic with a significant health impact, and clinical trials that aim to discover an effective vaccine are ongoing. Potential vaccines currently under development include genetically modified viruses, which are classified as GMOs [2,3]. Given the public health emergency caused by the COVID-19 outbreak, on July 15, 2020, the European Parliament and the EU Council granted a temporary derogation from the environmental requirements to allow clinical trials with GMOs intended to treat or prevent COVID-19 to start as soon as possible, without the delays generated by the different national implementations of environmental Directives 2001/18/EC and 2009/41/EC and their diverse requirements [4,5]. Although these two directives aim to ensure the protection of human health and the environment through the assessment of the risks posed by the deliberate release or contained use of GMOs, it has been decided that the protection of public health—through accelerating the deployment of a COVID-19 vaccine—prevails in this unprecedented situation.

Pivotal trials with promising candidates will be conducted in several countries, and without this measure, European clinical trials could fall behind those of the US or China, delaying early access to these product candidates. The derogation will apply as long as COVID-19 is regarded as a public emergency, but sponsors should implement appropriate measures to minimize the foreseeable negative environmental impact resulting from the release of the investigational medicinal product into the environment. Compliance with Good Manufacturing Practices and an ERA of the product will still be mandatory before marketing authorization is granted.

This temporary derogation has been very controversial. On the one hand, some expert groups have pointed out that this measure could be irresponsible since the development of vaccines based on GMO viruses might involve risks to human health and the environment, and these risks are not necessarily covered by the general safety protocols aimed at protecting participants [6]. On the other hand, supporters of the measure argue that a clinical study with only small quantities of an investigational product and a limited number of patients should not have a significant cumulative effect on the environment. The same argument can be found in US environmental regulations [7], whereby most investigational products are categorically excluded from the requirement to submit an ERA, but this principle has not been applied in the EU thus far, and massive trials including thousands of participants are expected for phase 3 studies with these vaccine candidates. One of the potential measures that could have been taken is to shorten the period to get the authorization for COVID-19 clinical trials, as was suggested by the Netherlands, which is the second Member State with the highest number of experimental GMO medicinal products approved under deliberate release [8]. However, this proposal does not solve the time-consuming process of preparing and submitting multiple applications with different requirements to several EU Member States.

Finally, this temporary derogation could also be seen as unfair to other products and/or disease areas. There are promising advanced therapies and vaccines under development consisting of GMOs, targeting severe orphan indications for pediatric populations to highly prevalent diseases such as HIV and cancer, the latter being one of the top

10 causes of death in the EU and the second leading cause of death globally [9]. These products still have to deal with the intricacies of these environmental procedures and the delays this implies for the starting of clinical studies in the EU, ultimately postponing patients' early access to these products.

### Conclusions

Attempts to streamline environmental procedures among EU Member States have so far been unsuccessful. With the temporary derogation from the environmental requirements for products intended to treat or prevent COVID-19, the bottleneck the environmental legislation represents in the EU for the development of innovative GMO-based medicines has become even more evident. Further efforts are needed to centralize or rationalize this procedure, with the main objective of enabling patients to benefit from innovative medicines for a variety of diseases as soon as possible.

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### Author Contributions

Conception and design of the study: CIL. Acquisition of data: CIL. Analysis and interpretation of data: CIL. Drafting or revising the manuscript: CIL. The author approved the final article.

### References

- [1] Iglesias-Lopez C, et al. Hurdles of environmental risk assessment procedures for advanced therapy medicinal products: comparison between the European Union and the United States. *Crit Rev Toxicol*. 2019;49(7):580–96.
- [2] Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* 2020;396(10249):467–78.
- [3] Mercado NB, Zahn R, Wegmann F, Loos C, Chandrashekar A, Yu J, et al. Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques. *Nature* 2020. [cited 2020 Sep 2];1–11. Available from <https://www.nature.com/articles/s41586-020-2607-z>.
- [4] Communication from the Commission to the European Parliament the European Council the Council and the European Investment Bank. In: EU Strategy for COVID-19 vaccines; 2020. [cited 2020 Sep 2]. Available from [https://ec.europa.eu/info/sites/info/files/communication-eu-strategy-vaccines-covid19\\_en.pdf](https://ec.europa.eu/info/sites/info/files/communication-eu-strategy-vaccines-covid19_en.pdf).
- [5] Official Journal of the European Union. In: Regulation (EU) 2020/1043 of the European Parliament and of the Council of 15 July 2020 on the conduct of clinical trials with and supply of medicinal products for human use containing or consisting of genetically modified organisms intended to treat or prevent coronavirus disease (COVID-19); 2020. [cited 2020 Sep 2]. Available from <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32020R1043&from=EN>.
- [6] Commissie Genetische Modificatie. In: COGEM advice concerning the proposal by the EC to suspend the environmental risk assessment of clinical trials for the treatment or prevention of COVID-19; 2020. [cited 2020 Sep 2]. Available from <https://cogem.net/app/uploads/2020/07/200624-01-Advice-concerning-the-proposal-by-the-EC-to-suspend-the-environmental-risk-assessment-of-clinical-trials-for-the-treatment-or-prevention-of-COVID-19.pdf>.
- [7] Center for Biologics Evaluation and Research. In: Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products: Guidance for Industry, Food and Drug Administration; 2015. [cited 2020 Sep 2]. Available from: <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidance>.
- [8] De Rijksverheid Voor Nederland. In: Scheme for Temporary Regulations on Alternative Treatment Gene Therapy Applications for Gene Therapy in Connection with Combating COVID-19; 2020. [cited 2020 Sep 2]. Available from: <https://www.rijksoverheid.nl/documenten/regelingen/2020/03/30/bijlage-1-spoedregeling-ggo-i-v-m-coronavirus>.
- [9] World Health Organization. Top 10 causes of death; 2018. WHO Fact Sheets. [cited 2020 Sep 2]. Available from: [https://www.who.int/gho/mortality\\_burden\\_disease/causes\\_death/top\\_10/en/](https://www.who.int/gho/mortality_burden_disease/causes_death/top_10/en/)